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(54) Title: SOLID ORAL DOSAGE FORMS OF AZABICYCLO DERIVATIVES

(57) Abstract: The present invention relates to solid dosage forms for oral administration of an azabicyclo derivative or its pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs and metabolites; and processes for the preparation of such solid dosage forms. The solid dosage forms can be characterized as having excellent content uniformity.

# Description

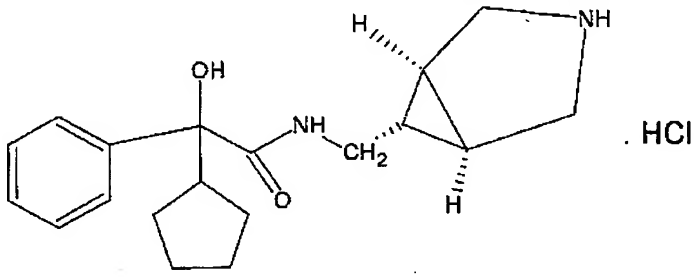
# SOLID ORAL DOSAGE FORMS OF AZABICYCLO DERIVATIVES

## Technical Field

[1] The present invention relates to solid dosage forms for oral administration of an azabicyclo derivative or its pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs and metabolites; and processes for the preparation of such solid dosage forms, wherein the solid dosage forms have excellent content uniformity.

## Background Art

[2] PCT application WO 2004/005252 filed by Ranbaxy Laboratories Ltd. discloses compound (I) and its pharmaceutically acceptable solvates, esters, enantiomers, di-astereomers, N-oxides, polymorphs and metabolites. Chemically, it is known as (2R)-(1alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo[3.1.0]hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride. The application also discloses processes for the preparation of the said compound.

[3] 


[4] Compound (I)

[5] Compound (I) is a muscarinic receptor antagonist with high affinity towards M3 receptors and may be useful as a safe and effective therapeutic or prophylactic agent for the treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through or associated with muscarinic receptors. Accordingly, the diseases or disorders may include diseases or disorders of the (a) respiratory system such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, and the like; (b) urinary system which induce such urinary disorders as urinary incontinence, lower urinary tract symptoms (LUTS), etc.; and (c) gastrointestinal system such as irritable bowel syndrome, obesity, diabetes and gas-trointestinal hyperkinesis, and the like.

[6] Because of its high potency, compound (I) is therapeutically effective at micromolar concentrations and needs to be administered at a very low dosage level.

However, the dispensing of a drug at low dose involves many complexities at the operational level, e.g., formulating the dosage form. In most cases, a major problem is to achieve content uniformity in a solid preparation. Failure to maintain the uniformity of drug content, e.g., if uniformity is not strictly assured, may result in an unforeseen accident by overdose or end up delivering a sub-therapeutic dose.

[7] One method for ensuring content uniformity of a low dose drug in a dosage form is by formulating the dosage form by wet granulation. Apart from ensuring content uniformity, wet granulation also provides better compressibility, improved flow properties, enhanced drug release and improved appearance. Being a wet process, wet granulation also reduces losses due to dust and minimizes exposure of the drug to the operator.

[8] We have discovered that pharmaceutical compositions of compound (I) having excellent content uniformity can be prepared by wet granulating a blend of excipients by a solution of compound (I).

## Disclosure

[9] Summary of the Invention

[10] In one general aspect there is provided a solid dosage form for oral administration comprising (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo[3.1.0] hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)] and a pharmaceutically acceptable carrier. The solid dosage form has excellent content uniformity.

[11] Embodiments of the solid dosage form may have one or more of the following features. For example, the solid dosage form may be prepared by granulating a blend of excipients with a solution of compound (I). The pharmaceutically acceptable carrier may be one or more excipients selected from diluent, binder, disintegrant, lubricant and glidant.

[12] The diluent may be one or more of lactose, dextrose, sucrose, fructose, maltose, mannitol, erythritol, sorbitol, xylitol, lactitol, microcrystalline cellulose, dicalcium phosphate, tribasic calcium phosphate, calcium sulphate and calcium carbonate. The diluent may be present in an amount ranging from about 50% to about 95% by weight of the composition.

[13] The binder may be one or more of corn starch, pregelatinised starch, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxyvinyl polymers and acrylates. The binder may be present in an amount ranging from about 1% to about 15% w/w by weight of the composition.

[14] The disintegrant may be one or more of cross-linked carboxymethylcellulose sodium, cross-linked polyvinylpyrrolidone, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, low-

substituted hydroxypropyl cellulose and alginates. The disintegrant may be present in an amount ranging from about 1% to about 10% w/w by weight of the composition.

[15] The lubricant may be one or more of talc, magnesium stearate, zinc stearate, calcium stearate, sodium stearyl fumarate and stearic acid. The glidant may be one or more of talc and colloidal silicon dioxide. The lubricant and/or glidant may be present in an amount ranging from about 0.1% to about 2% by weight of the composition.

[16] The pharmaceutically acceptable carrier may further include one or more of sweetener, coloring agent and flavoring agent. The solid dosage form may be a capsule or a tablet.

[17] In another general aspect there is provided as a process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)]. The process includes:

[18] a) blending one or more excipients selected from one or more of diluent, binder and disintegrant;

[19] b) granulating the blend with a solution of compound (I);

[20] c) drying and sizing the granules;

[21] d) blending the granules with one or more of lubricant, glidant, sweeteners, flavoring agents and coloring agents; and

[22] e) processing the granules into a dosage form.

[23] Embodiments of the process may include one or more of the features described above.

[24] In another general aspect there is provided a process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)]. The process includes:

[25] a) preparing a bed of excipients comprising one or more of diluent, binder and disintegrant;

[26] b) wetting the bed with a solvent;

[27] c) granulating the bed with a solution of compound (I);

[28] d) drying and sizing the granules;

[29] e) blending the granules with one or more of lubricant, glidanty, sweeteners, flavoring agents and coloring agents; and

[30] f) processing the granules into a dosage form.

[31] Embodiments of the process may include one or more of the features described above.

[32] In another general aspect there is provided a process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)]. The process includes:

[33] a) preparing a bed of excipients comprising one or more of diluent, binder and disintegrant;

[34] b) granulating the blend by uniformly spraying an atomized solution of compound (I);

[35] c) drying and sizing the granules;

[36] d) blending the granules with one or more of lubricant, glidant, sweeteners, flavoring agents and coloring agents; and

[37] e) processing the granules into a dosage form.

[38] Embodiments of the process may include one or more of the features described above.

[39] In another general aspect there is provided a process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)]. The process includes:

[40] a) fluidizing a bed of excipients comprising one or more of diluent, binder and disintegrant;

[41] b) granulating the blend with a solution of compound (I) and optionally further granulating with a binder solution;

[42] c) drying and sizing the granules;

[43] d) blending the granules with one or more of lubricant, glidant, sweeteners, flavoring agents, and coloring agents; and

[44] e) processing the granules into a dosage form.

[45] Embodiments of the process may include one or more of the features described above.

[46] In another general aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary or gastrointestinal systems mediated through or associated with muscarinic receptors, the method comprising administering to the animal or human a solid dosage form of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)] and a pharmaceutically acceptable carrier, wherein the solid dosage form has excellent content uniformity.

[47] Embodiments of the method may include one or more of the following features or the features described above. For example, the solid dosage form may be prepared by granulating a blend of excipients with a solution of compound (I).

[48] The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

[49] Detailed Description of the Invention

[50] The term 'compound (I)' as used herein includes pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs and metabolites of compound (I). Although compound (I) is a hydrochloride salt, other water-soluble pharmaceutically acceptable salts can also or instead be used and are within the scope of this invention. Compound (I) as described herein is used in a therapeutically effective amount in the solid dosage forms. The term 'therapeutically effective amount' intends to describe a dose of compound (I) that is effective for the treatment or prophylaxis of a disease or disorder of the respiratory, urinary and/or gastrointestinal systems. The dose may range from 0.01 μg to 20 mg of compound (I) per unit dosage form.

[51] The term 'content uniformity' or 'uniformity in content' as used herein is intended to describe solid dosage forms that pass the content uniformity test as described in the U.S. Pharmacopoeia (USP). The USP states that 'the requirements for dosage uniformity are met if the amount of active ingredient in not less than 9 out of the 10 dosage units as determined by content uniformity method lies within the range of 85.0% to 115.0% of label claim and no unit is out side the range of 75.0% to 125.0% of the label claim and the relative standard deviation (RSD) of the 10 dosage units is less than or equal to 6.0%.'

[52] The solid dosage forms as described herein are meant for oral administration and may be utilized in the form of granules, tablets or capsules. They may be ingested directly, or dispersed in water or other suitable vehicle prior to administration. Tablets may be of the rapidly disintegrating type, which disintegrate in the oral cavity, and can be taken with or without water. Capsules may be of the hard gelatin type.

[53] The solid dosage forms as described herein may include pharmaceutically acceptable excipients, including diluents, binders, disintegrants, lubricants and glidants.

[54] Diluents may be selected depending upon the compatibility with the active ingredient. Diluents that may be used include water-soluble as well as water-insoluble diluents or a mixture thereof. Water-soluble diluents may be exemplified, but are not limited to, saccharides like lactose, dextrose, sucrose, fructose, maltose; sugars like mannitol, erythritol, sorbitol, xylitol and lactitol; and the like. Water-insoluble diluents

may include but are not limited to cellulose derivatives like powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium carbonate and the like. The diluent may be used in an amount ranging form about 50% to about 95% by weight of the solid dosage form.

[55] Binders are generally used in a solid dosage form to impart cohesive properties to a powdered blend. Binders that may be used are selected from the group comprising starch derivatives like corn starch and pregelatinised starch, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxyvinyl polymers like carbomers, acrylates like Eudragits and other such materials routinely used in the art of solid dosage form manufacturing. The binder may be present in an amount varying from about 1% to about 15%, more particularly from about 5% to about 12% by weight of the solid dosage form.

[56] Disintegrants play a major role in the disintegration of solid dosage forms. The disintegrant may be selected from cross-linked carboxymethylcellulose and its sodium salt, cross-linked polyvinylpyrrolidone, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, low-substituted hydroxypropyl cellulose, alginates and the like. Particularly suitable disintegrants include cross-linked carboxymethylcellulose sodium. The amount of the disintegrant may vary from 1% to 10% by weight of the solid dosage form.

[57] Lubricants may be selected from the group consisting of talc, magnesium stearate, zinc stearate, calcium stearate, sodium stearyl fumarate and stearic acid. Glidants may be selected from talc, colloidal silicon dioxide, and the like. The lubricant and glidant may be used in a concentration of 0.1% to 2% by weight of the solid dosage form. The solid dosage forms as described herein may also include additional excipients like sweeteners, flavoring agents and coloring agents.

[58] The solid dosage forms as described herein are prepared by wet granulation method. The solution of compound (I) may be prepared in a solvent such as water or a mixture of water and a non-aqueous solvent. Excipients consisting of one or more diluent, binder and disintegrant are blended in a rapid mixer granulator and the blend subsequently granulated with the solution of compound (I). The mixture is kneaded until granulation is complete. The granules are then dried in a fluid bed drier and passed through a screen of suitable size. The dried granules are mixed with glidant and lubricant and either filled into capsules of suitable size or compressed into tablets using appropriate tooling. It was observed that partial granulation of the blend, so that a part of the excipient blend is converted into granules while a part is left ungranulated, yields tablets having rapid disintegration properties.

[59] It has been observed that the amount of water to be used in granulation is important and should be carefully optimized. The ratio of the weight of blend to the weight of

water is about 1:1.5 and more particularly about 1:1.1 to 1:1.2.

[60] One specific problem that is encountered while preparing the solid dosage forms, particularly dosage forms having a strength of less than 10 μg, by the wet granulation method as described above, is the desorption of water on the surface of the granules. Such a condition hinders the attainment of content uniformity in the dosage form. For overcoming this problem, the method described above may be slightly modified to include wetting of the excipients prior to granulation. One or more of diluent, binder and disintegrant are blended in a rapid mixer granulator to form a bed of excipients. The bed is then wetted with a solvent, such as water, prior to granulation. After wetting, the bed is then granulated with the solution of compound (I) and the granules are dried and sized. The dried granules are mixed with the glidant and lubricant and either filled into capsules of suitable size or compressed into tablets using appropriate tooling.

[61] The granulation may also be carried out using a spray granulation technique in which the bed of excipients, as prepared above, is sprayed upon by a solution of compound (I). The solution is atomized with the use of compressed air and spraying may be done using conventional equipments available, such as a spray gun. The mixture is continuously agitated as the granulation advances. The granules that are obtained are dried, sized and filled into capsules of suitable size or compressed into tablets using appropriate tooling.

[62] Fluidized bed granulation may also be used for carrying out wet granulation. The excipients consisting of one or more diluent, binder and disintegrant are introduced in the fluid bed granulator and fluidized. The solution of compound (I) is sprayed onto the fluidized bed from the top against the air-flow by means of a spray nozzle. Optionally, a part of the binder in the form of a solution can additionally be sprayed to form granules. The granules obtained are filled into capsules of suitable size or compressed into tablet using appropriate tooling.

[63] In one embodiment, capsules of compound (I) are prepared by dissolving compound (I) in water to form an aqueous solution; granulating a blend of diluent, binder and disintegrant with the solution; drying and sizing the granules; blending the granules with a lubricant and a glidant; and filling the granules in capsules of suitable size.

[64] In another embodiment, tablets of compound (I) are prepared by dissolving compound (I) in water to form an aqueous solution; granulating a blend of diluent, binder and disintegrant with the solution; drying and sizing the granules; blending the granules with a lubricant and a glidant; and compressing the granules into tablets using appropriate tooling.

[65] In another embodiment, tablets of compound (I) are prepared by dissolving

compound (I) in water to form an aqueous solution; partially granulating a blend of diluent, disintegrant, binder and optionally a second diluent, coloring agent and flavoring agent with the solution so that a part of the excipient blend is converted into granules while a part is left ungranulated; drying the partially granulated excipient blend and further mixing with a diluent, disintegrant, lubricant, glidant, coloring agent and flavoring agent; and compressing the granules into tablets using appropriate tooling.

[66] In another embodiment, capsules of compound (I) are prepared by preparing a bed of excipients consisting of diluent, binder and disintegrant; wetting the bed with water; granulating the bed with an aqueous solution of compound (I) under continuous mixing; drying and sizing the granules; blending the granules with a lubricant and a glidant; and filling the granules in capsules of suitable size.

[67] In another embodiment, capsules of compound (I) are prepared by preparing a bed of excipients consisting of diluent, binder and disintegrant; preparing a solution of compound (I); atomizing and uniformly spraying the solution over the bed of excipients along with continuous mixing and agitation to form granules; drying and sizing the granules; blending the granules with a lubricant and a glidant; and filling the granules in capsules of suitable size.

[68] In another embodiment, a solid dosage form of compound (I) is prepared by preparing a bed of excipients consisting of diluent, binder and disintegrant in a fluidized bed granulator; spraying aqueous solution of compound (I) over the bed of excipients and granulating the blend partially; spraying a binder solution and granulating the mixture completely; sizing the granules; blending the granules with a lubricant and a glidant; and filling the granules in capsules of suitable size.

[69] The invention described herein is further illustrated by the following examples but these should not be construed as limiting the scope of the invention:

[70] **Examples 1 to 6**

[71]

| S/N | Ingredients | Quantity in mg/capsule | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| 1 | Compound I | 0.01 | 0.025 | 0.1 | 0.4 | 1.0 | 2.0 |
| 2 | Microcrystalline cellulose | 34.19 | 85.475 | 85.40 | 28.67 | 71.68 | 143.35 |
| 3 | Croscarmellose sodium | 1.2 | 3.0 | 3.0 | 1.02 | 2.55 | 5.1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4 | Pregelatinised starch | 4.0 | 10 | 10.0 | 3.4 | 8.5 | 17.0 |
| 5 | Purified water | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| 6 | Magnesium stearate | 0.2 | 0.5 | 0.5 | 0.17 | 0.425 | 0.85 |
| 7 | Colloidal silicon dioxide | 0.2 | 0.5 | 0.5 | 0.17 | 0.425 | 0.85 |
| 8 | Talc | 0.2 | 0.5 | 0.5 | 0.17 | 0.425 | 0.85 |
| | Total weight (in mg) | **40** | **100** | **100** | **34** | **85** | **170** |

[72] **Procedure:** Compound (I) was dissolved in water. Microcrystalline cellulose, croscarmellose sodium and pregelatinized starch were sifted and blended in a rapid mixer granulator. The blend was granulated with the solution of compound (I). The granules were dried in a fluid bed dryer and subsequently sized in a mill using an appropriate screen. The sized granules were sifted and mixed with magnesium stearate, colloidal silicon dioxide and talc. The final blend obtained was filled into capsules of appropriate size.

[73] **Example 7**

[74] **Procedure:** The final blend prepared by the procedure as given above using the composition of Example 6 was compressed into tablets using appropriate tooling.

[75] **Example 8**

[76]

| S/N | Ingredients | Quantity in mg/capsule |
|---|---|---|
| 1 | Compound 1 | 0.10 |
| 2 | Lactose monohydrate | 54.40 |
| 3 | Microcrystalline cellulose | 30.00 |
| 4 | Croscarmellose sodium | 3.00 |
| 5 | Pregelatinised starch | 10.00 |
| 6 | Purified water | q.s. |
| 7 | Magnesium stearate | 1.00 |
| 8 | Talc | 1.00 |
| 9 | Colloidal silicon dioxide | 0.50 |
| | Total weight | **100 mg** |

[77] **Procedure:** Compound (I) was dissolved in water. Lactose monohydrate, micro-crystalline cellulose, croscarmellose sodium and pregelatinized starch were sifted and blended in a rapid mixer granulator. The blend was granulated with the solution of compound (I). The granules were dried in a fluid bed dryer and subsequently sized in a mill using an appropriate screen. The sized granules were sifted and mixed with magnesium stearate, colloidal silicon dioxide and talc. The final blend obtained was filled into capsules of appropriate size.

[78] **Example 9**

[79]

| S/N | Ingredients | Quantity in mg/capsule |
|---|---|---|
| 1 | Compound 1 | 0.0025 |
| 2 | Lactose monohydrate | 21.7975 |
| 3 | Microcrystalline cellulose | 12.00 |
| 4 | Croscarmellose sodium | 1.20 |
| 5 | Pregelatinised starch | 4.00 |
| 6 | Purified water | q.s. |
| 7 | Magnesium stearate | 0.40 |
| 8 | Talc | 0.40 |
| 9 | Colloidal silicon dioxide | 0.20 |
| | Total weight | **40 mg** |

[80] Procedure: Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and pregelatinised starch were sifted and blended in a rapid mixer granulator at slow speed to form a bed. Purified water was added in a quantity sufficient enough to wet the bed of excipients and mixed with the excipients. The aqueous solution of Compound (I) was added to the wet bed and mixed with kneading to obtain granules. The granules were dried and subsequently sized in a mill using an appropriate screen. The sized granules were sifted and mixed with magnesium stearate, colloidal silicon dioxide and talc. The final blend obtained was filled into capsules of appropriate size.

[81] **Example 10**

[82] **Procedure:** The final blend prepared by the procedure as described in Example 9 was compressed into tablets using appropriate tooling.

[83] **Example 11**

[84]

| S/N | Ingredients | Quantity in mg/capsule |
|---|---|---|

| | | |
|---|---|---|
| 1 | Compound 1 | 0.0025 |
| 2 | Microcrystalline cellulose | 34.1975 |
| 3 | Croscarmellose sodium | 1.20 |
| 4 | Pregelatinised starch | 4.00 |
| 5 | Purified water | q.s. |
| 6 | Magnesium stearate | 0.20 |
| 7 | Talc | 0.20 |
| 8 | Colloidal silicon dioxide | 0.20 |
| | Total weight | **40 mg** |

[85] **Procedure:** Microcrystalline cellulose, croscarmellose sodium and a part of the pregelatinised starch were introduced into a GlattTM, fluidized, and partially granulated by spraying an aqueous solution of Compound (I) on the bed through a nozzle situated above the bed. The remaining amount of pregelatinised starch was dissolved in water and the solution was then sprayed on the mixture to complete granulation. The granules thus obtained were sized and filled into capsules of appropriate size.

[86] **Example 12**

[87]

| S/N | Ingredients | Quantity in mg/capsule |
|---|---|---|
| 1 | Compound 1 | 0.0025 |
| 2 | Spray-dried mannitol | 46.9775 |
| 3 | Microcrystalline cellulose | 30.00 |
| 4 | Croscarmellose sodium | 5.00 |
| 5 | Pregelatinised starch | 10.00 |
| 6 | Aspartame | 6.50 |
| 7 | Color | 0.01 |
| 8 | Flavor | 0.01 |
| 9 | Purified water | q.s. |
| 10 | Magnesium stearate | 0.50 |
| 11 | Talc | 0.50 |
| 12 | Colloidal silicon dioxide | 0.50 |
| | Total weight | **100 mg** |

[88] **Procedure:** Spray-dried mannitol, microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, aspartame, color and flavor were sifted and blended. The blend was partially granulated by an aqueous solution of compound (I) and the granules were dried. Magnesium stearate, colloidal silicon dioxide, talc and the remaining amount of microcrystalline cellulose, croscarmellose sodium, color and flavor were added to the partially granulated mixture and the mixture was subsequently compressed into tablets using appropriate tooling.

[89] The content uniformity of the capsules prepared as per the details given in Examples 1 to 6 were tested as per the method specified for content uniformity testing in USP. The results of this testing showed that the content uniformity of these capsules were well within the specified limits (Table 1).

[90] **TABLE 1**: Percentage Relative Standard Deviation (% RSD) for capsules of Examples 1-6

[91]

| **Dosage strength** | **% RSD*** |
|---|---|
| 0.01 mg | 4.09 |
| 0.025 mg | 3.21 |
| 0.1 mg | 3.36 |
| 0.4 mg | 1.95 |
| 1.0 mg | 1.97 |
| 2.0 mg | 1.24 |

[92] *As per USP, % RSD for 10 dosage units should not be more than 6 %

[93] While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

# Claims

[1] A solid dosage form for oral administration comprising (2R)-(1 alpha, 5alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)] and a pharmaceutically acceptable carrier, wherein the solid dosage form has excellent content uniformity.

[2] The solid dosage form according to claim 1, wherein the solid dosage form is prepared by granulating a blend of excipients with a solution of compound (I).

[3] The solid dosage form according to claim 1, wherein the pharmaceutically acceptable carrier comprises one or more excipients selected from diluent, binder, disintegrant, lubricant and glidant.

[4] The solid dosage form according to claim 3, wherein the diluent comprises one or more of lactose, dextrose, sucrose, fructose, maltose, mannitol, erythritol, sorbitol, xylitol, lactitol, microcrystalline cellulose, dicalcium phosphate, tribasic calcium phosphate, calcium sulphate and calcium carbonate.

[5] The solid dosage form according to claim 3, wherein the diluent is present in an amount ranging from about 50% to about 95% by weight of the composition.

[6] The solid dosage form according to claim 3, wherein the binder comprises one or more of corn starch, pregelatinised starch, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxyvinyl polymers and acrylates.

[7] The solid dosage form according to claim 3, wherein the binder is present in an amount ranging from about 1% to about 15% w/w by weight of the composition.

[8] The solid dosage form according to claim 3, wherein the disintegrant comprises one or more of cross-linked carboxymethylcellulose sodium, cross-linked polyvinylpyrrolidone, sodium starch glycolate, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, low-substituted hydroxypropyl cellulose and alginates.

[9] The solid dosage form according to claim 3, wherein the disintegrant is present in an amount ranging from about 1% to about 10% w/w by weight of the composition.

[10] The solid dosage form according to claim 3, wherein the lubricant comprises one or more of talc, magnesium stearate, zinc stearate, calcium stearate, sodium stearyl fumarate and stearic acid.

[11] The solid dosage form according to claim 3, wherein the glidant comprises one or more of talc and colloidal silicon dioxide.

[12] The solid dosage form according to claim 3, wherein the lubricant and/or glidant is present in an amount ranging from about 0.1% to about 2 % by weight of the

composition.

[13] The solid dosage form according to claim 3, wherein the pharmaceutically acceptable carrier further comprises one or more of sweetener, coloring agent and flavoring agent.

[14] The solid dosage form according to claim 1, wherein the solid dosage form comprises a capsule or a tablet.

[15] A process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)], the process comprising:

a) blending one or more excipients selected from one or more of diluent, binder and disintegrant;

b) granulating the blend with a solution of compound (I);

c) drying and sizing the granules; d) blending the granules with one or more of lubricant, glidant, sweeteners, flavoring agents and coloring agents; and e) processing the granules into a dosage form.

[16] A process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)], the process comprising:

a) preparing a bed of excipients comprising one or more of diluent, binder and disintegrant;

b) wetting the bed with a solvent;

c) granulating the bed with a solution of compound (I);

d) drying and sizing the granules;

e) blending the granules with one or more of lubricant, glidanty, sweeteners, flavoring agents and coloring agents; and

f) processing the granules into a dosage form.

[17] A process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)], the process comprising:

a) preparing a bed of excipients comprising one or more of diluent, binder and disintegrant;

b) granulating the blend by uniformly spraying an atomized solution of compound (I);

c) drying and sizing the granules;

d) blending the granules with one or more of lubricant, glidant, sweeteners,

flavoring agents and coloring agents; and

e) processing the granules into a dosage form.

[18] A process for the preparation of a solid oral dosage form for oral administration of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl]-2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)], the process comprising:

a) fluidizing a bed of excipients comprising one or more of diluent, binder and disintegrant;

b) granulating the blend with a solution of compound (I) and optionally further granulating with a binder solution;

c) drying and sizing the granules;

d) blending the granules with one or more of lubricant, glidant, sweeteners, flavoring agents, and coloring agents; and

e) processing the granules into a dosage form.

[19] A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary or gastrointestinal systems mediated through or associated with muscarinic receptors, the method comprising administering to the animal or human a solid dosage form of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] - 2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride [compound (I)] and a pharmaceutically acceptable carrier, wherein the solid dosage form has excellent content uniformity.

[20] The method of treatment or prophylaxis of claim 19, wherein the solid dosage form is prepared by granulating a blend of excipients with a solution of compound (I).

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(54) Title: SOLID ORAL DOSAGE FORMS OF AZABICYCLO DERIVATIVES

(57) Abstract: The present invention relates to solid dosage forms for oral administration of an azabicyclo derivative or its pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs and metabolites; and processes for the preparation of such solid dosage forms. The solid dosage forms can be characterized as having excellent content uniformity.

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/052104

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2004/005252 A (RANBAXY LABORATORIES LIMITED; SALMAN, MOHAMMAD; MEHTA, ANITA; SARMA, P) 15 January 2004 (2004-01-15) cited in the application claims 6,7 | 1,3-14, 19 |
| A | page 3, line 8 - line 13 | 2,15-18, 20 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 7 July 2006 | 20/07/2006 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax (+31-70) 340-3016 | VON EGGELKRAUT, S |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/052104

**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 19 and 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

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